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VEGF-VEGFR pathway seems to be the best target in hepatic epithelioid hemangioendothelioma: A case series with review of the literature

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ABSTRACT

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor originating from endothelial cells. Clinical aspect of the disease covers a wide spectrum from a low-grade tumor to a fatal cancer. Most common sites of EHE are reported as lung, liver and bone. Hepatic EHE (HEHE) is a clinical form with an incidence of less than 1 person in a million. Due to rarity of the disease, there is no standard therapy established. Surgery and liver transplantation still seem to be the best approach if possible. However, most of the patients present with unresectable or metastatic disease. Many conventional chemotherapeutic agents and antiangiogenic drugs have been reported previously in the literature with inconsistent outcomes. Here we report 4 cases of HEHE, who benefit distinctly from anti-VEGF treatments in different settings. While combination of paclitaxel and bevacizumab resulted in partial response in 3 patients, one of them also achieved long-term disease stabilization with bevacizumab maintenance with no adverse event. Two of the patients had clear benefit from pazopanib during the course of disease. One patient was treated with thalidomide

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for 18 months with stable disease, and is still being followed without any treatment. Although targeting VEGF-VEGFR pathway seems to be the best approach in HEHE, randomized studies are urgently needed to support these findings.

ARTICLE INFO

Keywords: Epithelioid hemangioendothelioma; hepatic; VEGF; bevacizumab

Introduction

Epithelioid hemangioendothelioma (EHE) is a very rare malignant vascular neoplasm arising from endothelial cells. Although it is usually known to be a low-grade vascular sarcoma, in fact it has a variable natural course. Clinical behavior can vary from an indolent course to a fatal disease.[1] While the disease affects mostly middle-aged patients, among them there seems to be a female predominance.[2] Liver, lung and bone are the most reported primary tumor sites.[3] Hepatic EHE (HEHE) is a clinical form of the disease and mostly presents with multifocal lesions.[4] The low incidence of EHE and unpredictable course make it difficult to establish a standard management. For localized disease, surgery seems to be the best approach, however there is still no consensus on multifocal or metastatic disease. Liver transplantation (LTx), radiofrequency ablation, transarterial chemoembolization, radiotherapy, chemotherapy, targeted therapies and also follow-up without any treatment are options with limited data mostly based on individual clinical experience.[5,6] Herein, we present 4 different cases of metastatic HEHE who benefit distinctly from anti-VEGF treatments in the disease course and review the literature on this uncommon tumor (Table 1).

Case presentations

Case 1

A 46-year-old man presented with right upper quadrant pain for 2 months on January 2011. Physical examination was unremarkable; he did not have any chronic diseases or family history of cancer or other diseases. Magnetic resonance imaging (MRI) of the abdomen demonstrated multiple hepatic lesions, which of the largest being 2 cm in size. All tumor markers (alpha-fetoprotein [AFP], carcinoembryonic antigen [CEA], CA19-9) were within normal range, viral hepatitis markers were negative, and neither endoscopy nor colonoscopy showed any pathologic findings. Tru-cut biopsy of one of the liver lesions finally diagnosed HEHE. Thoracic computed tomography (CT) and FDG-PET/CT were performed to complete staging, and also revealed a 1.5 cm spiculated nodule in upper lobe of left lung. Another biopsy from lung nodule was planned to exclude a primary lung cancer however the patient did not accept. Hepatic lesions were considered unresectable, and there was no living donor for LTx. Therefore, 4 cycles of CAP protocol (cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, cisplatin 50 mg/m^2, all drugs on day 1 every 3 weeks) were administered as first-line therapy. Unfortunately, liver lesions progressed, so paclitaxel and bevacizumab regimen was initiated with the dose of 80 mg/m^2 paclitaxel on days 1, 8, and 15 and 7.5 mg/kg bevacizumab on day 1, every 3 weeks. Following 8 cycles, there was a partial response in liver lesions thus maintenance bevacizumab was continued for 1 year. On March 2013, owing to the progression of hepatic lesions, this time gemcitabine and bevacizumab treatment was started with the dose of 1000 mg/m^2 gemcitabine on days 1, 8 and 7.5 mg/kg bevacizumab on day 1, every 3 weeks. After 12 cycles, gemcitabine was stopped with the stable disease and maintenance bevacizumab was again given for additional 2 years. On May 2016, the patient had a serious chest pain, therefore bevacizumab was stopped while he still had

Table 1
Demographic features, therapeutic data and overall survival of our reported cases of hepatic epiteloid hemangioendothelioma.

Patient	Gender	Age	Primary Tumor Site	Metastatic Sites	Systemic Therapy (PFS in Months)	Overall Survival Month (mo)
1	Male	46	Liver	Lung	1. CAP* (3 mo) 2. Paclitaxel-bevacizumab, maintenance bevacizumab (20 mo) 3. Gemcitabine—bevacizumab, maintenance bevacizumab (44 mo) 4. Capecitabine (5 mo) 5. Paclitaxel-bevacizumab, maintenance bevacizumab (22 mo) 6. Pazopanib (6 mo and still ongoing)	108 mo (alive)
2	Female	51	Liver	Lung	1. Paclitaxel (3.5 mo) 2. Pazopanib (7 mo and still ongoing)	13 mo (alive)
3	Male	39	Liver	Bone	1. Paclitaxel-bevacizumab (5 mo) 2. Gemcitabine (4 mo) 3. Cisplatin (2 mo)	15 mo (exitus)
4	Male	21	Liver	Lung	1. Thalidomide (27 mo) 2. Paclitaxel-bevacizumab** (47 mo) 3. Interferon alfa-2b***	74 mo (alive)

* CAP: cyclophosphamide, doxorubicin, cisplatin
** Although paclitaxel-bevacizumab regimen resulted in partial regression, patient rejected to have more chemotherapy. Therefore, interferon alfa-2b was started as maintenance.
*** Patient could tolerate interferon alfa-2b for only 2 weeks and stopped treatment.

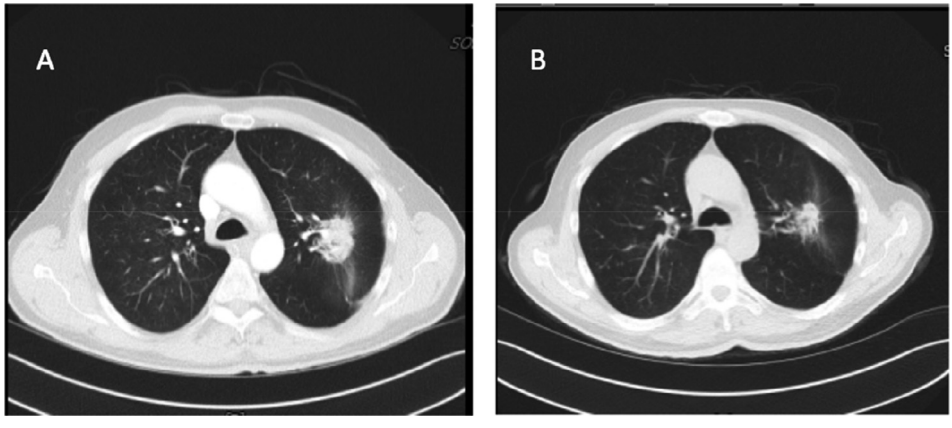

Fig. 1. (A) Pretreatment thoracic CT on July 2017; (B) After 3 cycles of paclitaxel plus bevacizumab therapy, a prominent regression of left lung lesion (case 1).

stable disease. There was no pathological finding on cardiac examinations, and he was started to be followed up without any treatment. After 6 months of therapy break, the lesion in upper lobe of left lung increased 50% in size (26×23 mm), and biopsy was offered again to patient but he rejected. Capecitabine was started with the total dose of 2000 mg/m^2/day, however at the end of 3 months, lung lesion progressed markedly with becoming 35×33 mm in size while hepatic lesions were stable. In terms of previous good and long-lasting response with paclitaxel and bevacizumab, we started the same treatment with the same doses and after 3 cycles there was a prominent regression of lung nodule (Fig 1). Therefore, we continued the combination

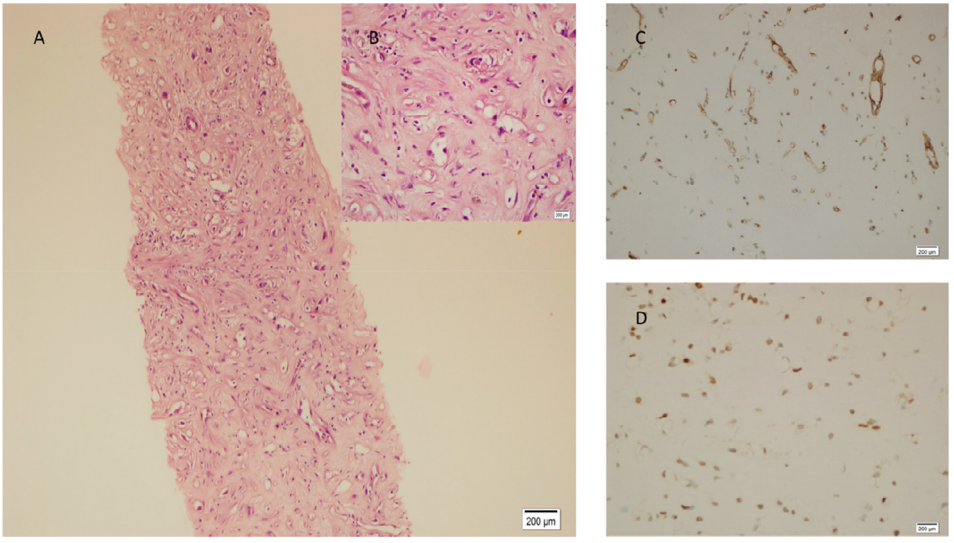

Fig. 2. Liver biopsy specimen of case 2: (A, B) Spindled epithelioid cells embedded in a myxoid matrix (H&E, × 200) (C). CD34 positivity in immunohistochemistry stains. (D). FLI-1 positivity in immunohistochemistry stains.

therapy for 4 more months and then maintenance bevacizumab with no drug toxicity. On July 2019, due to progression of lung nodule from 30 × 23 mm to 41 × 34 mm, pazopanib 800 mg/day was started and following 3 months of therapy, the disease seemed to be stable on PET-CT. The patient is still on pazopanib treatment.

Case 2

On December 2018, a 51-year-old woman presented with left inguinal pain lasting for 1 month. No pathologic findings were present on physical exam. Blood and urine tests were all unremarkable. She had no other comorbidities or significant family history. The abdominal ultrasonography detected multiple hepatic lesions. To complete staging, FDG-PET/CT was performed and revealed a 53 × 40 mm malignant lesion throughout 2nd and 3rd hepatic segment (SUVmax 9.0) and multiple hypodense lesions in segment 4A and 6, the largest being 21 mm, without increased metabolic activity, and also a metastatic 18 mm nodule in lower lobe of right lung. A tru-cut biopsy of liver was performed and pathological examination resulted in diagnosis of HEHE (Fig 2). Owing to unresectable disease, paclitaxel 80 mg/m^2 weekly was initiated as first-line treatment. After 4 cycles, PET-CT showed progression of liver lesions with the largest one in segment 2-3 becoming 57 × 40 mm with SUVmax of 13.6 and all other lesions showing hypermetabolism with SUVmax of 8.0 while lung nodule was stable. Therefore, pazopanib was started as second-line of treatment with the dose of 800 mg per day. Following 4 months of treatment, PET-CT showed partial regression of liver lesions and stable lung nodule. She is still on the same dose of pazopanib treatment with no serious adverse events.

Case 3

A 39-year-old man presented with hemoptysis and back pain for 3 months. He had no previous history of any disease, injury or operation. Also no family history of cancer was obtained. On September 2018, thoracic CT detected 55 mm area of increased density compatible with pneumonia in lower lobe superior segment of right lung reaching to posterior pleura, metastatic

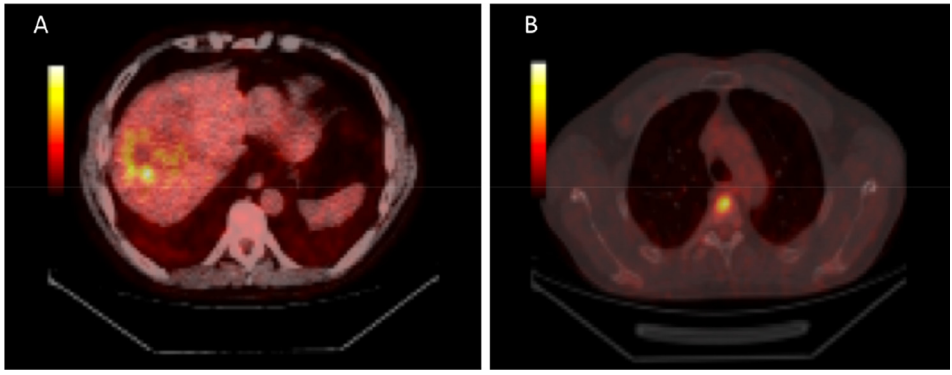

Fig. 3. The baseline FDG-PET/CT of case 3: (A) 66 × 37 mm liver lesion in segment 8 with SUVmax of 5.5; (B) T3 vertebral body lesion with SUVmax 5.5.

lesions in liver and a lytic lesion in T4 vertebral body. Abdomen MRI showed multiple liver metastasis the largest of which being 8.5 × 7.5 cm in segment 8. He was treated 2 weeks with antibiotics. FDG-PET/CT was performed in order to find the primary focus of cancer and multiple liver (SUVmax 5.5) and bone metastasis (SUVmax 5.5) were reported while no metabolic activity was detected in lungs and mediastinal lymph nodes as a sign of recovery of pneumonia (Fig 3). Due to increased metabolic activity detected in ascending colon, colonoscopy was performed and it was reported as normal. Pathological diagnosis of tru-cut biopsy of liver revealed HEHE. On account of metastatic disease, systemic treatment with paclitaxel (80 mg/m^2 on days 1, 8, and 15) and bevacizumab (7.5 mg/kg on day 1) was started and repeated in every 3 weeks. Also, zoledronic acid infusion with the dose of 4 mg was initiated for bone metastasis. Following the first cycle, the total bilirubin level, mainly direct form, started to increase rapidly. Therefore, magnetic resonance cholangiography was performed and it detected dilatation of intrahepatic bile ducts mainly due to obstruction with an associated hepatic mass. Total and direct bilirubin levels were 25 mg/dL and 16 mg/dL, respectively when percutaneous transhepatic cholangiography was performed and a biliary drainage catheter was placed. Since bilirubin levels dropped down more than 50% only in 1 week after catheter replacement, chemotherapy was started again with the same dose. After 1 more cycle, bilirubin levels were within normal range and 4 cycles of paclitaxel and bevacizumab could be given to the patient with a good response. On April 2019, FDG-PET/CT showed a new hepatic lesion in segment 4B while there appeared to be regression in bone lesions. Therefore, gemcitabine 1000 mg/m^2 on days 1, 8 and 15 every 4 weeks was started as second-line therapy. At the end of 4 cycles, FDG-PET/CT showed newly diagnosed peritoneal carcinomatosis and marked ascites. At the time of progression, bilirubin level also started to increase again, thus we decided to treat the patient with cisplatin 50 mg/week however he could only tolerate 2 doses due to clinical deterioration. Following this, he was admitted to hospital with biliary drainage catheter infection and acute renal failure. Unfortunately, he died 15 months after diagnosis.

Case 4

On November 2013, a 21-year-old man admitted to hospital with cough and dyspnea. He had no relevant past medical history or family history. Physical examination showed all normal findings. Abdominothoracic CT demonstrated multiple noncalcified nodules in both lungs compatible with metastasis, the largest of which was 6 mm and also multiple hepatic lesions, the largest of which was 36 × 26 mm in 8th segment of right lobe. Tru-cut biopsy of liver was reported as HEHE. Thereafter, he was treated with thalidomide for almost one and a half year with stable disease. However, he stopped treatment and was lost to follow-up until February

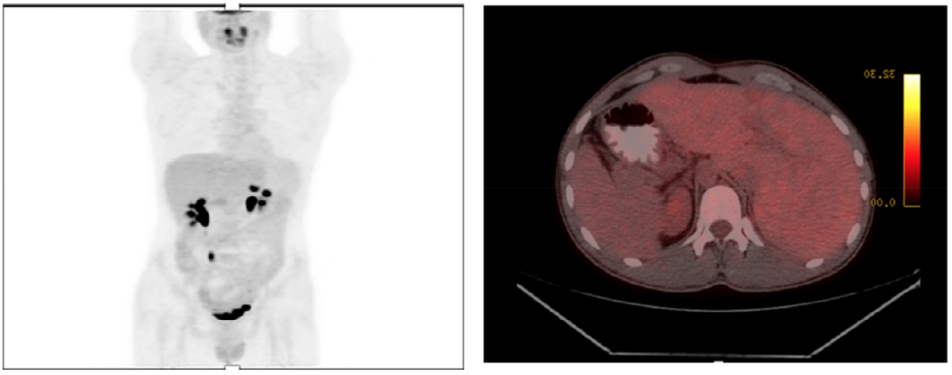

Fig. 4. The last FDG-PET/CT of case 4 performed on November 2019, with no metabolically active lesion appears.

2016. FDG-PET/CT was performed and detected a new 1.4 cm lytic lesion in the right clavicle with a SUVmax of 3.1 and multiple progressed liver and lung metastasis. Systemic treatment was initiated as paclitaxel (80 mg/m^2 on days 1, 8, and 15) and bevacizumab (7.5 mg/kg on day 1), and repeated in every 3 weeks. Between March and July 2016, 4 cycles of treatment were administered and on August 2016, abdominothoracic CT showed 30% regression of lung nodules and 15% regression of some liver lesions, while some other liver lesions and clavicular lesion were stable in size. Since the patient rejected to have more chemotherapy, interferon alfa-2b was started as maintenance however only after 2 weeks patient stopped treatment due to adverse effect. We started to follow him up without any treatment and the last FDG-PET/CT performed on November 2019 did not show any metabolically active lesion (Fig 4). The patient is still on active surveillance and have a good medical condition.

Discussion

EHE is an extremely rare malignant vascular tumor among sarcoma family that can occur in soft tissue and visceral organs such as liver, lung, bone, spleen, stomach and hearth.[3] It was first described in 1982 by Weiss and Enzinger.[7] Clinical aspect of the disease covers a wide spectrum from a low-grade tumor to a lethal cancer. World Health Organization (WHO) also changed the classification of this disease in 2013 from a low-grade tumor and considered EHE as a malignant sarcoma of vascular origin such as angiosarcoma.[8] Mortality rates and aggressiveness of the disease differ by the localization of primary tumor. Worst outcome was reported for lung EHE followed by hepatic primary.[6] HEHE is a clinical entity with an incidence of less than 1 person in a million.[6] Ishak et al. first published their series of 32 patients with HEHE in 1984. Woman were more affected by the disease and both lobes of the the liver were often involved with tumor. They reported that 28% of the patients had extrahepatic metastases however prognosis was still better than angiosarcoma.[9] Owing to rarity of the disease, our limited knowledge about HEHE is coming from few published data including case reports, case series and some retrospective observational studies. Therefore, the optimal management of the multifocal disease is still challenging.

Radical hepatic resection with negative margins is the best and curative approach if feasible and related with best prognosis.[1,10] Five-year survival rate after resection was reported as 75%.[6] However, patients usually present with multifocal disease which makes surgery ineligible. Mehrabi et al. analyzed all published data on patients with HEHE (n = 434) between 1984-2005, and reported multifocal involvement of liver as 87% and only 13% of patients presented with a unifocal tumor. Extrahepatic metastases at the time of diagnosis was seen in 36.6% of patients, lung being the most metastatic site with a percentage of 8.5%, followed by regional lymph

nodes (7.7%), peritoneum (6.1%), and bone (4.9%).[6] LTx is the preferred treatment modality for multifocal unresectable hepatic disease, moreover HEHE is considered as a favorable indication for LTx.[11,12] Since the outcomes of patients with HEHE after LTx improved substantially regardless of extrahepatic disease, limited extrahepatic involvement is not an absolute contraindication anymore. Five-year survival after LTx was documented as ranging from 43% to 76% in different series in the literature.[13,14] However, lack of organ donation and long waiting lists in some countries make LTx an impracticable option. All our patients had multifocal disease in liver and also extrahepatic metastases (3 of them had lung and 1 had bone metastases) at the time of diagnosis. Hepatic resection was not an option and there remained no living organ donor for LTx. Therefore, we started with systemic treatment for all of them.

Given that HEHE is best treated with resection or LTx if possible,[4] systemic treatment remains an option for unresectable or metastatic HEHE with an unknown efficacy due to lack of randomized trials. There is also no standard approach established for systemic treatment. Data is mostly obtained from retrospective studies and case series, and chemotherapy based treatments were found to be related with worse outcomes.[4] Systemic treatment includes chemotherapy, immune therapy and targeted therapies.[15] Previous data on the efficacy of conventional chemotherapeutic agents remain controversial. Doxorubicin, paclitaxel and 5-fluorouracil appear to be the most used drugs in the literature. Morris et. al reported a case of a 33-year-old lady, initially misdiagnosed with cholangiocarcinoma and treated with combination of doxorubicin, 5-fluorouracil and vincristine successfully. Patient was free from any further problems after 10 years with a revised diagnosis of HEHE.[16] In another reported case of a 45-year-old man, doxorubicin treatment showed a remarkable regression of the lesions in liver and spleen.[17] However, combination of epirubicin and dacarbazine could not control the disease in another patient with stage 4 HEHE metastatic to both pleura and bone.[18] The largest retrospective study from Royal Marsden Hospital of 32 patients, reported the best response as stable disease with carboplatin plus paclitaxel, liposomal doxorubicin, ifosfamide plus doxorubicin, paclitaxel alone given for the first and second-line treatments.[1] One report documented a good response to liposomal doxorubicin in a patient diagnosed with bone metastatic HEHE.[19] Low-dose maintenance therapy of liposomal doxorubicin was also used with no toxicity in a patient who had partial regression to the standard dose.[20] Pinet et al. reported a long lasting complete response to carboplatin plus etoposide after 6 cycles in a patient of pleural EHE.[21]

Regarding the vascular base of this neoplasm, Stacher et al. showed high levels of vascular endothelial growth factor (VEGF) expression as expected.[22] Since then, many antiangiogenic drugs using this pathway have been investigated in different cases with variable outcomes. Bevacizumab, a monoclonal antibody against VEGF, has been applied alone or in combination with chemotherapy associated with inconsistent results. For instance, combination of bevacizumab with carboplatin-paclitaxel was reported to achieve a partial response in a patient with pulmonary EHE,[23] whereas the same treatment could not show any response in another case.[24] Furthermore, same combination resulted in reduction of the disease in a different patient with pulmonary EHE however, she died from a rare but serious complication of bevacizumab, cerebral infarct.[25] Kanemura et al. documented a case of EHE originated from pleura, and treated with carboplatin, pemetrexed and bevacizumab with an impressive reduction in the disease.[26] Bevacizumab monotherapy was also reported to achieve a long-term stabilization of a recurrent EHE of the spine without any adverse event.[27] Likewise, Merikas et al. documented the efficacy of bevacizumab monotherapy in their case series.[28] On the other hand, Lazarus et al. declared 2 cases of pleural EHE, both of whom progressed with paclitaxel-bevacizumab and combination of carboplatin, etoposide plus bevacizumab.[29] Nab-paclitaxel and bevacizumab regimen induced stable disease with a good clinical response in another patient with disseminated bone metastatic EHE.[30] A multicenter phase 2 trial of bevacizumab included 7 patients with EHE. Two of them experienced a partial response (29%) and other 4 (57%) were followed with stable disease.[31] In another published case of metastatic HEHE, capecitabine was initially given as a single agent for 1 year with stable disease and then bevacizumab was added to capecitabine with a good response.[32]

Tyrosine kinase inhibitors such as sorafenib, pazopanib, apatinib and sunitinib which inhibit different VEGF receptors have also been reported in EHE, as well.[33–36] A phase 2 study of sorafenib, demonstrated a promising efficacy in patients with EHE, with providing a nonprogression rate at 6 months as 38.4% (5 of 13 patients).[33] Pazopanib could control the disease in a patient with HEHE for almost 8 years.[34] In addition to Tyrosine kinase inhibitors, thalidomide and lenalidomide, which are considered to have both antiangiogenic and immunomodulatory effects, have been reported to be used for EHE in the literature previously. Two case reports documented partial response with thalidomide, and in one of which patient continued the drug for 109 months with minimal toxicity.[37,38] Sumrall et al. reported a patient with disseminated EHE, who had been treated with lenalidomide for approximately 6 years with stable disease.[39] "No treatment" is also a strategy, and has a role in management of EHE, particularly for asymptomatic patients.[2,4] Spontaneous resolution of EHE have been reported in a number of cases.[40]

In our case series of HEHE, combination of paclitaxel and bevacizumab resulted in partial response in 3 patients. Besides bevacizumab monotherapy as maintenance was successful to control the disease for a long time in 1 patient. Gemcitabine was also effective in combination with bevacizumab in 1 case, providing a long-lasting response which was followed by maintenance bevacizumab. Two of the patients had clear benefit from pazopanib, one of them showed partial response and the other was followed by stable disease. One patient was treated with thalidomide for almost one and a half year with stable disease, until he stopped treatment. Paclitaxel and bevacizumab regimen was successful to control the disease when progression of disease occurred after 8 months. However, patient rejected any kind of treatment and is still being followed by "no treatment" approach. Spontaneous resolution of the disease was detected similar to reported in the literature.

Conclusion

Our experience highlights the efficacy of anti-VEGF treatments in the management of EHE. The vascular origin of this tumor and high levels of VEGF expression appears to be the rationale behind using drugs that target VEGF-VEGFR pathway. However, randomized studies are urgently needed to support these findings and establish a standard algorithm.

CRediT authorship contribution statement

Tugba Akin Telli: Writing - original draft, Writing - review & editing. **Ilker Nihat Okten:** Writing - review & editing. **Tuğba Basoglu Tuylu:** Data curation, Investigation. **Nazim Can Demircan:** Data curation, Investigation. **Rukiye Arikan:** Data curation, Investigation. **Ozkan Alan:** Data curation, Investigation. **Ozlem Ercelep:** Data curation. **Tunc Ones:** Visualization. **Aysenur Toksoz Yildirim:** Visualization. **Faysal Dane:** Supervision. **Perran Fulden Yumuk:** Supervision.

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